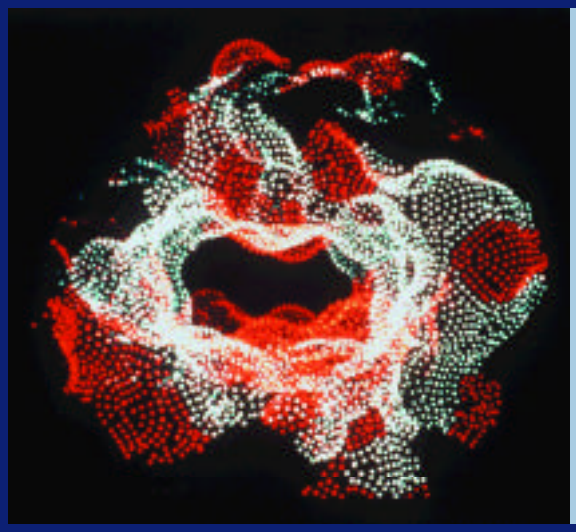
NIAID Research:
Stories of Discovery



NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

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NIAID Research: Stories of Discovery

February 1999

For Administrative Purposes Only

National Institute of Allergy and Infectious Diseases
National Institutes of Health

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Contents

Foreword

In its 50-year history, the National Institute of Allergy and Infectious Diseases (NIAID) has played a leading role in the fight against infectious microbes and diseases of the immune system. By supporting research in microbiology and immunology, NIAID has advanced our understanding of the basis for the molecular and genetic aspects of disease and provided insights that have contributed to the development of important new therapies, vaccines, and diagnostic tools. In just the past few years, investment in basic research has culminated in several important clinical advances. Institute-supported scientists joined other researchers in making landmark discoveries that were crucial to the development of new or improved vaccines to protect against rotaviral diarrhea, pertussis, and Lyme disease as well as new treatments for infection with the human immunodeficiency virus (HIV). Collaboration with partners in academia and industry helped convert basic research findings into new products, such as vaccines, that have benefited public health. NIAID-supported researchers continue to uncover new insights, such as the immune system mechanisms involved in HIV infection and transplant rejection, which promise to stimulate further progress in combating infectious and immunologic diseases. With continued commitment to basic research and effective partnerships, even greater accomplishments can be expected during the Institute's next 50 years.

Anthony S. Fauci, M.D.
Director
National Institute of Allergy
and Infectious Diseases

Introduction

Despite medical breakthroughs such as the development of antibiotics and vaccines, infectious diseases remain a major health threat around the world. Infectious diseases are the leading cause of death globally, killing more than 17 million people worldwide. Even in the United States, where good medical care and sanitation are available, infectious diseases are the third leading cause of death. The threat of new and reemerging diseases and the widespread development of resistance to standard antimicrobial drugs increase the urgency of developing new vaccines and treatments for infectious diseases. Immunologic diseases also exact a heavy toll on the health of people worldwide. Allergic diseases, including asthma, affect as many as 40 million Americans, and autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, affect approximately 9 million.

In fulfilling its mission to find ways to diagnose, treat, and prevent infectious and immunologic diseases, NIAID draws on a foundation of knowledge gained from basic research in immunology, microbiology, and infectious diseases. The Institute's sustained efforts in these fields have led to recent advances that promise immediate and future benefits to the health of people around the world.

Stories Behind the Headlines

When the mass media informs the public about new HIV treatments, improved vaccines, or other medical innovations, it seldom describes the many years of basic scientific research that made such progress possible. However, the first step in developing these medical advances often occurs in laboratories such as those at NIAID and universities around the world where Institute-supported scientists perform experiments to answer fundamental scientific questions about infectious microbes and the human immune system. Scientific knowledge gained through this basic research provides the foundation for designing new or improved vaccines, treatments, or diagnostics for conditions such as HIV/AIDS, malaria, and other infectious diseases; asthma and allergies; autoimmune diseases; and transplant rejection.

Similarly, the public seldom learns about the subsequent stages of development and testing that are needed before such products are proven both safe and effective. These stages include several phases of applied research to test new drugs, vaccines, and diagnostics in animals followed by clinical research to ensure safety and efficacy in humans. NIAID works to move promising medical innovations through these stages of research by collaborating with academia and private industry to enlist needed skills and resources. For example, partners in private industry provide expertise in product development and manufacturing.

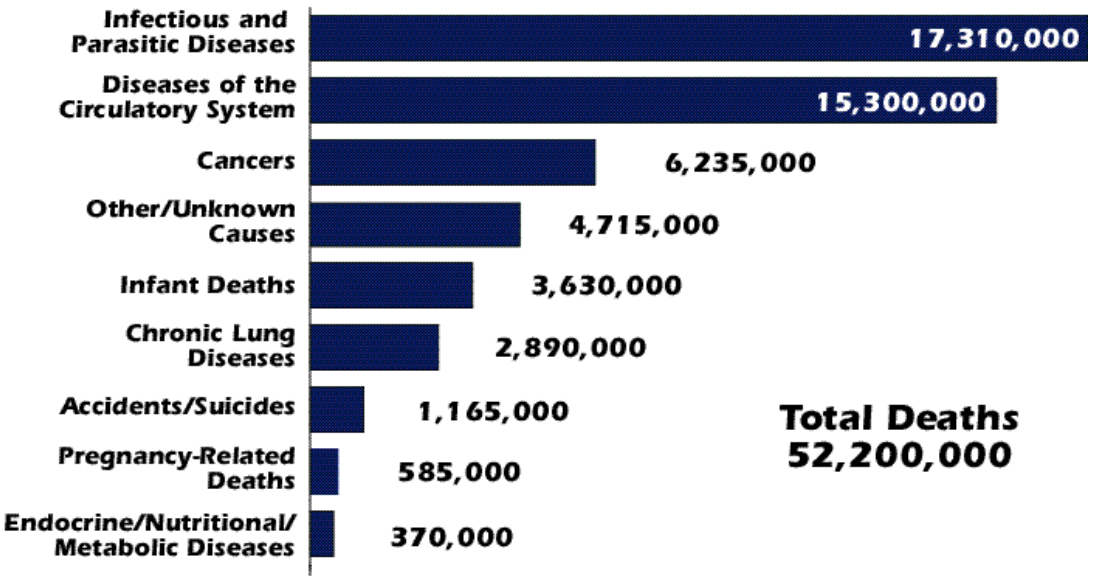
Commitment to Basic Research and Collaboration

This booklet presents six stories of scientific discoveries that will have a major impact on the health of Americans and other people around the world. Four of the stories are about NIAID-supported basic research efforts that led to the development of innovative vaccines or treatments that are now available to prevent or treat diseases affecting millions of people. Two other stories describe NIAID's role in discoveries that offer promising new avenues for the future development of much-needed therapies.

These stories highlight the importance of basic research and Government-industry partnerships to improvements in public health. For example, the three stories on new or improved vaccines illustrate how advances in understanding the immune system and the complex interactions between microbes and the body can lead to the design of novel vaccines. Similarly, basic research studies supported by NIAID, other National Institutes of Health (NIH) Institutes, and other Government agencies to learn more about HIV and the immune system response to the virus paved the way for the design of new combination therapies and are opening a new area of anti-HIV drug design. These stories demonstrate how NIAID, other NIH Institutes, and Government agencies, researchers in academia, and partners in industry collaborate to assist with the development, licensure, and marketing of important new products. Similar partnerships will be crucial to converting new insights about HIV-host interactions and immune tolerance into practical, new therapies.

These six stories of discovery represent just a few of the ways that NIAID-supported research is addressing global health problems. The final section on the Institute's research priorities highlights other areas in which NIAID is making valuable contributions to the fight against infectious and immunologic diseases.

Worldwide Causes of Death



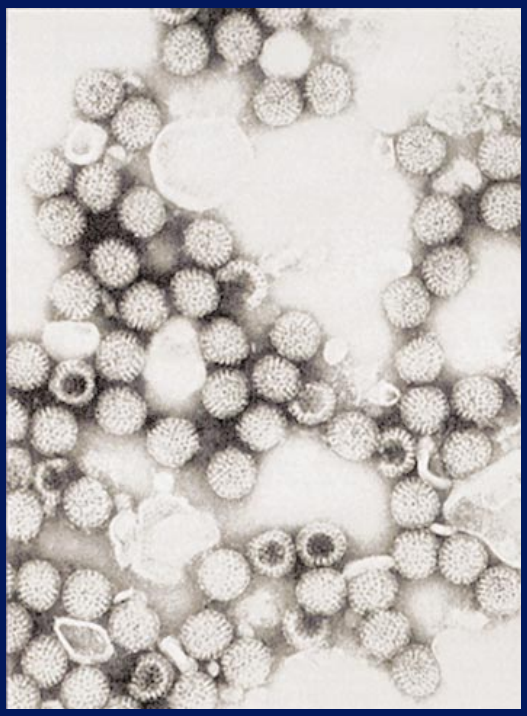
Even with advances in medical treatment and the discovery of antibiotics and other effective treatments, infectious and parasitic diseases are still the number one cause of death, accounting for approximately one-third of the deaths around the world.

Source: The World Health Report 1998, WHO

Rotavirus Vaccine: Preventing Severe Diarrheal Disease in Infants

By expanding our understanding of how microbes cause disease, research conducted and supported by NIAID has paved the way for the development of new vaccines that have reduced death and illness from infectious diseases. Most recently, NIAID scientists developed a vaccine against rotavirus, the cause of more than 2,000 childhood deaths worldwide *each day*. The new vaccine has the potential to reduce hospitalizations and deaths among infants, particularly in developing countries. This success story highlights the importance of applying basic research findings to the development of practical public health tools and of fostering collaboration with private industry to develop these products further.

Rotavirus



Identifying a Major Killer of Children

Twenty-five years ago, little was known about the causes of diarrhea, which kills an estimated 3 million infants and children worldwide every year. Although scientists knew that bacteria and parasites were possible culprits, these organisms could be implicated in only approximately 10 to 20 percent of all cases of diarrhea. Since the late 1960s, basic researchers at NIAID's Laboratory of Infectious Diseases have studied diarrheal diseases to determine how they are caused and how they are transmitted and to develop effective treatments and prevention strategies. In 1972, NIAID scientists identified the first virus that was shown to cause diarrhea. The next year, researchers in Australia discovered another virus in infants with severe diarrhea and named it "rotavirus" for its wheel-like shape. One year later, NIAID researchers were the first to identify rotavirus in the United States.

Over the next two decades, researchers studied rotavirus and made several important findings. They concluded that rotavirus is the single most important cause of life-threatening diarrhea in children younger than 2 years, affecting approximately 130 million infants and children worldwide. The symptoms of rotavirus infection develop quickly and include vomiting in addition to diarrhea. Children with severe cases may require hospitalization and, if inadequately treated, may become severely dehydrated and die. In the United States alone, rotavirus causes more than 3 million cases of childhood diarrhea each year, leading to an estimated 55,000 to 100,000 hospitalizations and 20 to 100 deaths.

Traditionally, it was thought that most cases of diarrhea could be prevented by improvements in hygiene and sanitation. However, such steps alone are insufficient since rotavirus can survive for long periods on hard surfaces such as toys and tables. The highly infectious virus probably is spread by the oral-fecal route and is not killed by standard disinfectants. Efforts to overcome the challenge posed by this hardy virus were aided by the researchers' discovery that most children have been infected with rotavirus by the age of 3 years. An infant's first bout of diarrhea from rotavirus is the most severe, with subsequent reinfections decreasing in severity. These findings indicated that infants gradually develop a partial immunity to the virus and that a vaccine might prevent disease.

Developing an Innovative Vaccine

Building on this fundamental knowledge about rotavirus, NIAID-supported researchers embarked on the development of a vaccine. During the 1970s, NIAID scientists analyzed the genetic material of rotavirus, identified important proteins produced by the genes, and determined the function of these proteins. Two proteins on the surface of the virus were found to be critical for triggering an immune response in the body against rotavirus. NIAID researchers focused on these proteins to develop a vaccine.

Scientists knew that although many strains of rotavirus exist, only four cause the majority of diarrhea cases in young children in the United States. NIAID researchers developed a vaccine (RRV-TV) designed to protect against these four strains of rotavirus. To create this vaccine, NIAID scientists pioneered a technique for combining the four viral strains in one oral vaccine. This innovative approach involved mixing three genetically altered human rotavirus strains and one strain of a monkey rotavirus to provide safe but comprehensive protection against this disease.

Transferring Technology to Private Industry

To help speed the further development, testing, and marketing of the rotavirus vaccine, NIAID signed a Cooperative Research and Development Agreement (CRADA) with Wyeth-Ayerst Laboratories in 1987. In the early 1990s, NIAID, the Centers for Disease Control and Prevention, Wyeth-Ayerst Laboratories, and nearly two dozen U.S. medical centers collaborated on studies to test the effectiveness and safety of the four-strain rotavirus vaccine. These studies showed that high doses of the RRV-TV vaccine, designed to protect against four strains of rotavirus, were very effective in preventing severe, dehydrating rotavirus disease. In 1995, researchers determined that breast-feeding did not interfere with the effectiveness of the rotavirus vaccine, an important finding for ensuring good nutrition in infants.

However, diarrhea caused by rotavirus kills thousands of children in developing countries every year and the question remained whether the vaccine would be as effective in these nations. To address this question, NIAID collaborated in 1996 with investigators in Venezuela to test the RRV-TV vaccine. One year later, study results showed that the rotavirus vaccine was safe and reduced severe diarrhea in children by 88 percent and severe dehydration by 77 percent. This study was the largest and most successful trial to date of a rotavirus vaccine among children in a developing country. The vaccine eventually was tested in approximately 18,000 infants in the United States and abroad and was licensed in the United States in August 1998.

Reaping Public Health and Economic Benefits

In the United States, studies indicate that widespread vaccination of infants against rotavirus will be cost-effective and will decrease the number of physician visits and hospitalizations, which

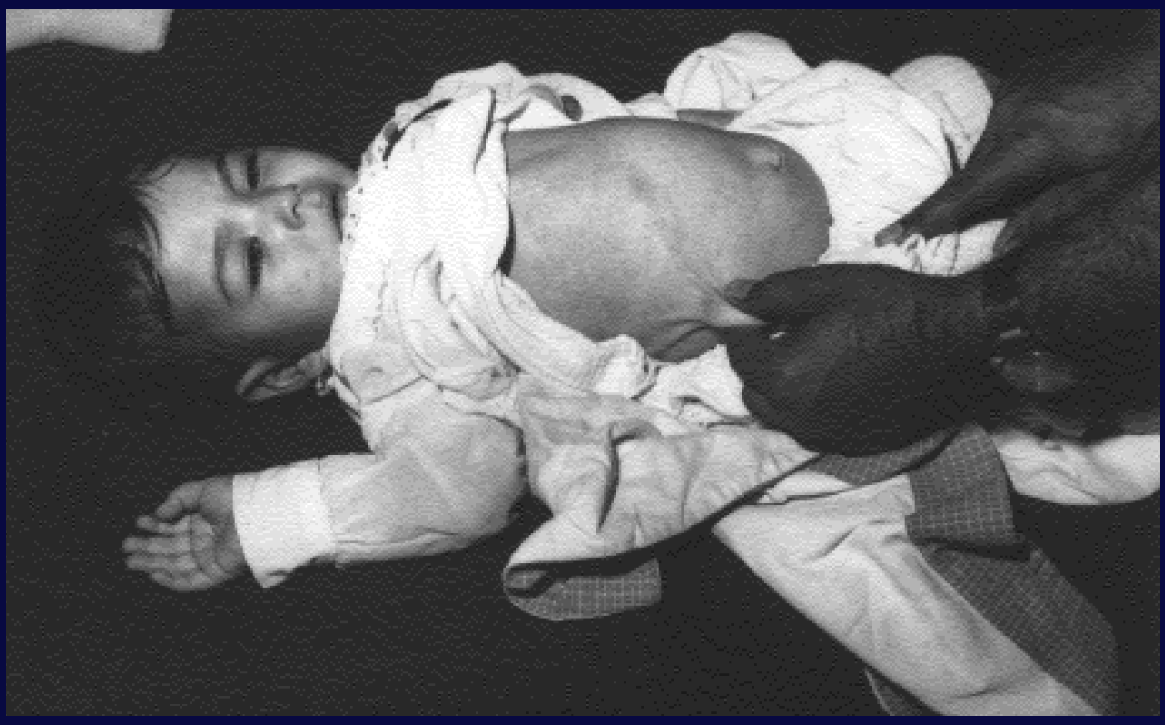
contribute to the estimated $500 million annual health care costs associated with rotaviral diarrhea. The worldwide benefits of the vaccine could be even greater. The World Health Organization estimates that use of the rotavirus vaccine could reduce the number of deaths caused by diarrhea among infants and young children by 30 percent, saving the lives of as many as 1 million children each year.

Research for Further Progress

The development of the rotavirus vaccine is a major step forward and has laid the foundation for the next steps in vaccine development for diarrheal diseases. Future challenges include improving the vaccine so that it prevents severe episodes of disease in more children. Also, effectiveness in Africa and Asia needs to be tested.

Current efforts are directed at improving the effectiveness of rotavirus vaccines and further decreasing unwanted side effects of vaccination. If successful, a less expensive vaccine that is more widely acceptable should result. Newer vaccine technologies are also being applied to the development of new rotavirus vaccines. Approaches using DNA vaccines, virus-like particles, edible vaccines, and multi-valent vaccines are in the development stage, and some are in early clinical studies. Continued worldwide surveillance for rotavirus will enable NIAID to track possible emergence of new strains of rotavirus that would require a different vaccine. NIAID is contributing to surveillance activities by providing necessary materials to researchers in the field.

A Doctor Examining a Dehydrated Child



Dehydration is the primary cause of morbidity and mortality from diarrheal diseases. It can be reversed through oral rehydration therapy or, if more serious, through hospitalization and intravenous fluids. Although these therapies are effective, they are not readily available or widely used in many parts of the developing world.

Credit: Dr. D. Mahalanabis, World Health Organization

Improved Pertussis Vaccines: Enhancing Protection

In addition to its efforts to develop new vaccines, NIAID devotes substantial resources to developing improved vaccines that are more effective and have fewer side effects than currently used vaccines. Using powerful new technologies and knowledge gained from basic research, NIAID has been instrumental in the development of second-generation vaccines that protect against important childhood diseases. The story of NIAID's role in the development of acellular pertussis vaccines for infants exemplifies the public health benefits of the Institute's investment in basic research and its international collaborations with partners in government, industry, and academia. The new acellular (non-whole cell) pertussis vaccines are safer and cause fewer side effects because they use select parts of the disease-causing microbe that are important for immunity. The traditional whole-cell vaccines, by contrast, use the entire, killed cell of the infectious microbe.

The First Pertussis Vaccine

Pertussis, also known as whooping cough, is a highly contagious respiratory disease that affects more than 50 million people worldwide and causes an estimated 350,000 deaths each year, primarily among infants. Before pertussis vaccines were available, more than 200,000 cases of the disease were reported annually in the United States. The search for a pertussis vaccine began in 1906, when two French bacteriologists isolated *Bordetella pertussis*, the bacterium that causes infection. In the 1940s, experimental vaccines using whole-cell *B. pertussis* were successful in mimicking infection and producing a protective immune response in humans. The first whole-cell pertussis vaccine was licensed for use in the United States in 1948. Subsequent widespread use of the vaccine contributed to a dramatic decline in the U.S. incidence of the disease, which reached an all-time low of approximately 1,010 cases in 1976.

Although the whole-cell vaccine was extremely effective in controlling pertussis, it was associated with side effects ranging from fever and inflammation at the injection site to rare but more serious events such as seizures. Concerns about these side effects discouraged some parents from having their children immunized against pertussis. As a result, by the early 1980s the number of pertussis cases was increasing in the United States.

The side effects associated with the whole-cell pertussis vaccine were also commonly seen with whole-cell vaccines for other types of bacteria. These bacteria had something in common with *B. pertussis*. They all belonged to a subgroup called gram negative bacteria. Specific molecules unique to the gram negative bacteria were believed to be responsible for the inflammatory response that caused the side effects.

In response to public concerns about the safety of the whole-cell vaccine, NIAID set out to develop an improved vaccine that would be equally effective but that caused fewer and less harmful side effects. As an initial step in this process, NIAID-supported scientists began to conduct more basic research to thoroughly analyze the biology of *B. pertussis* and to learn more about how the bacterium causes disease.

New Vaccine Technology

As early as 1975, basic researchers at NIAID's Rocky Mountain Laboratories were characterizing the properties of a protein called pertussigen, or pertussis toxin (PT), secreted by *B. pertussis*, which triggered an immune response. PT became the cornerstone of second-generation pertussis vaccine development, and all future acellular pertussis vaccines contained an inactivated form of PT that was no longer capable of causing harmful effects. With information gained from this basic research, NIAID scientists and other researchers began to design acellular vaccines that excluded *B. pertussis* bacterium molecules that were likely to cause side effects and used only purified *B. pertussis* products, such as pertussis toxin or other antibody-producing components, that would invoke an immune response against the bacterium while producing minimal side effects.

Testing the New Vaccine

In the early 1980s, NIAID-supported researchers began collaborating with vaccine manufacturers and investigators around the world to speed the development of acellular pertussis vaccines. A large Swedish study supported by NIAID in the mid-1980s tested the disease-preventing effectiveness of two acellular pertussis vaccines. In 1989, the Institute invited manufacturers of acellular pertussis vaccines to participate in further studies. The following year, NIAID initiated a multicenter trial that compared the effectiveness of 13 acellular pertussis vaccine candidates with two whole-cell vaccines. The trial was the first to compare acellular and whole-cell vaccines among infants. It was also a significant collaborative venture involving government agencies, manufacturers in five countries, and the NIAID-supported network of university-based Vaccine and Treatment Evaluation Units.

Encouraging findings from the multicenter study prompted NIAID to support two large clinical trials in Sweden and Italy. Begun in 1991-1992, these landmark international studies demonstrated that acellular vaccines are as effective in protecting infants against pertussis but cause fewer side effects than whole-cell vaccines. These positive results were instrumental in the 1996 licensure of the first children's diphtheria-tetanus-pertussis (DTaP) vaccine that includes an acellular, rather than a whole-cell, pertussis component. NIAID's collaborations with the Food and Drug Administration, the Centers for Disease Control and Prevention, and the pharmaceutical industry were crucial to the expedited approval of DTaP vaccines. Widespread use of these safer, well-tolerated vaccines is expected to promote rates of immunization against pertussis and reduce related illness and death.

NIAID is now applying the success of acellular pertussis vaccines for children to the development of similar vaccines for adolescents and adults. Because vaccine-induced immunity weakens after 6 to 10 years, adults have become a major source of pertussis transmission, particularly to unvaccinated infants. Adult formulations being developed with NIAID support could increase booster immunization of adolescents and adults, thereby helping to reduce the incidence of pertussis in young infants as well as adults. The Institute also is continuing efforts to improve pertussis vaccines further by finding ways to reduce the number of vaccine doses required and to lengthen the period of immunity produced by the vaccine.

Lyme Disease Vaccine: Preventing an Emerging Disease

A major priority of NIAID is meeting the threat of emerging infectious diseases. NIAID support for basic research is a key strategy for identifying the organisms responsible for new diseases and for providing information needed to develop diagnostic tests, treatments, and vaccines. The value of NIAID's contribution to the prevention and treatment of emerging diseases is exemplified by the story of the development of a vaccine for Lyme disease. NIAID-supported scientists discovered the microbe that causes Lyme disease and contributed other insights that led to the production of a safe and effective vaccine for the prevention of Lyme disease. This achievement emphasizes the importance of basic research in providing knowledge to mount a timely response to emerging diseases.

More than 100,000 cases of Lyme disease have been reported in the United States, and the incidence is increasing each year. Approximately 12,500 new cases were diagnosed in 1997. Lyme disease can be difficult to diagnose because it is easily mistaken for other ailments, and existing laboratory tests can be inaccurate. Although Lyme disease can be treated successfully in the early stages with antibiotics, patients

Lyme Disease: The Timeline of Its Discovery and the Development of a Vaccine

1975	First cases of Lyme disease reported.
1981	Microbe identified.
1989	The outer surface protein, OspA, found and cloned.
Early 1990s	Antibodies to OspA found in many chronic Lyme disease patients.
1990-1992	Vaccinations with rOspA found to protect mice against Lyme disease infection.
1992-1995	Vaccinations with rOspA tested in other animals.
1995	Lyme vaccine found safe and effective in persons with Lyme disease.
1995-1998	Vaccine found safe and effective in people without Lyme disease.
1998	FDA approves Lyme vaccine.

who go untreated or do not respond to antibiotics may develop significant complications months or years later. These problems may include painful arthritis, especially in the knees, nervous system difficulties, and heart complications. Treatment of early-stage Lyme disease alone costs an estimated $60 million a year in the United States.

Identification of an Emerging Disease

Lyme disease was first recognized in 1975, when researchers investigated several cases of arthritis among children living in Lyme, Connecticut. The researchers suspected that an unidentified infectious microbe caused the illness, because the sick children lived near each other and became ill at the same time. Many of the children also recalled being bitten by a tick before becoming ill, and some developed a distinctive skin rash just before other symptoms appeared. From these clues, the researchers suspected that deer ticks, common insects the size of a pinhead, were involved in transmitting an unknown infectious microbe.

Discovery of the Culprit

In 1981, as NIAID researchers were examining deer ticks for microbes that cause tick-borne disease, the researchers serendipitously found a new microbe. This spiral-shaped bacterium later was named *Borrelia burgdorferi*, after the NIAID scientist, Dr. William "Willie" Burgdorfer, who discovered the microbe. The next year, NIAID researchers at the Rocky Mountain Laboratories isolated *B. burgdorferi* from deer ticks and developed a method to grow it in the laboratory. When scientists mixed the bacterium with blood from people who had recovered from Lyme disease, they found that the microbes reacted with a particular antibody produced during the immune response to infection. Such antibodies were not present in people who had never had Lyme disease, indicating that *B. burgdorferi* was the likely cause of Lyme disease. In further tests, rabbits developed both a rash similar to the typical Lyme disease rash as well as the same type of immune response generated after being bitten by ticks infected with *B. burgdorferi*. The following year, NIAID-supported scientists found *B. burgdorferi* in the blood and other tissues of patients with Lyme disease.

In the mid-1980s, NIAID-supported and other researchers began to decipher the makeup of the surface proteins of the microbe and made an important discovery. They identified and analyzed a protein on the outer surface of *B. burgdorferi*. This protein, outer surface protein A (OspA), causes an immune response in humans. NIAID researchers then cloned the

A Rapid Response to Another Emerging Disease: Avian H5N1 Influenza

The people of Hong Kong and the world medical community were recently alarmed by an unexpected outbreak of an influenza that usually affects only birds but began to appear in people in Hong Kong. Fortunately, NIAID has conducted research on respiratory viruses for decades and had the specific antisera in its reagent repository. The reagent was used to quickly develop test kits for detecting the virus. NIAID also supported the rapid production of a vaccine against the avian influenza virus for use by medical personnel at risk of catching the disease. Thus, building on years of basic research, NIAID, in collaboration with the CDC, the WHO, and other agencies, was able to quickly address critical public health needs brought about by the outbreak.

gene for OspA and created recombinant OspA (rOspA). rOspA is an artificially manufactured version of the natural OspA. This technique allows the protein to be produced in large enough quantities for use in vaccine studies. In the early 1990s, NIAID investigators and their collaborators found that antibodies against OspA were able to neutralize *B. burgdorferi* in infected ticks, thus preventing the transmission of infection from ticks to humans. As basic research continued, other outer surface proteins as well as other parts of *B. burgdorferi* were identified as potential candidate vaccines.

Development of a Vaccine

Since these surface proteins produce an immune response, researchers began to consider using them to develop vaccines against Lyme disease. In the early 1990s, NIAID-supported researchers developed an OspA-based vaccine that protected mice from infection.

Between 1995 and 1998, a vaccine based on rOspA, the component first made by NIAID investigators, was tested by SmithKline Beecham in humans. The vaccine was proven safe and effective for preventing infection for people between the ages of 15 and 70. In 1998, the FDA approved a vaccine against Lyme disease, LYMErix, produced by SmithKline Beecham.

Research for Further Progress

Continued research is essential for further progress against Lyme disease. More work is needed to improve diagnostic tests, to understand why some patients' symptoms disappear while other patients' symptoms persist, to develop a vaccine for children, and to improve treatment for people with chronic Lyme disease. NIAID is supporting further research on the underlying mechanisms of *B. burgdorferi* through studies of the immune response to infection and to vaccination. The Institute is funding studies to improve the understanding and treatment of chronic Lyme disease. These and other investigations will ultimately contribute to a greater understanding of Lyme disease and the development of ways to prevent and treat this emerging infectious disease.

The Ticks That Carry Lyme Disease

The tick, Ixodes scapularis, *that is the most common carrier of Lyme disease in the American Northeast and Midwest. The female (left) is larger than the male (right).*

New Treatments for HIV Infection: Prolonging and Improving Life

When AIDS was first recognized in 1981, patients with the disease were unlikely to live longer than a year or two. Today, advances in understanding the human immunodeficiency virus (HIV) and how it causes AIDS have helped scientists to develop an effective arsenal of drugs that, when used in combination, can help many people with HIV disease live longer and healthier lives. The addition of a new class of anti-HIV drugs to combination therapies has contributed to the first drop in the U.S. AIDS death rates since the beginning of the epidemic. (See the graph on AIDS death rates.) The story of this achievement highlights the pivotal contributions of both basic research and the Institute's collaborations with academia and industry to develop effective treatments for HIV disease.

Since HIV was identified in 1983, NIAID-supported scientists have led efforts to understand how the virus attacks the immune system and causes disease. This research demonstrated that substantial amounts of HIV are present, primarily in the lymphoid tissue, from the earliest stages of infection; that levels of HIV typically increase as HIV disease progresses; and that HIV remains infectious and actively replicates even while trapped and hidden in immune cells. Such basic research discoveries provide the rationale for using drugs that delay or prevent HIV disease by suppressing HIV replication.

Early Anti-HIV Treatments

For several years, the only drugs available for treating HIV infection were nucleoside analogue reverse transcriptase (RT) inhibitors. These drugs interfere with the action of a specific HIV enzyme (RT) involved in the replication cycle of HIV. The first anti-HIV drug, zidovudine (AZT), was originally developed in 1964 as a possible cancer treatment but was found to be ineffective against tumor cells. However, collaboration between the National Cancer Institute and the pharmaceutical company Burroughs Wellcome led to the discovery in the early 1980s of AZT's ability to suppress HIV replication in the test tube and paved the way for clinical trials of AZT.

Burroughs Wellcome, with input from NIH and the Food and Drug Administration, successfully conducted testing of AZT in HIV-infected individuals. Subsequently, NIAID's AIDS Clinical Trials Group (ACTG) conducted several clinical trials in partnership with industry to test four other nucleoside RT inhibitors: zalcitabine (ddC), didanosine (ddI), stavudine (D4T), and lamivudine (3TC). All five drugs are now licensed in the United States. Additional ACTG studies demonstrated the benefits of AZT therapy for preventing mother-to-infant transmission of HIV and for lowering the risk for developing AIDS in persons with HIV infection.

Unfortunately, HIV rapidly develops resistance to these and other anti-HIV drugs. Researchers have attacked the problem of drug resistance—which is particularly harmful because of HIV's high rate of replication and mutation—by using regimens of multiple anti-HIV drugs. NIAID-supported researchers were among the first to show (in 1995) that treatment with combinations of AZT and other nucleoside analogue RT inhibitors was more effective than treatment with AZT alone. In addition, combining 3TC with AZT slowed the virus from developing resistance to AZT and, in some cases, restored AZT sensitivity in patients

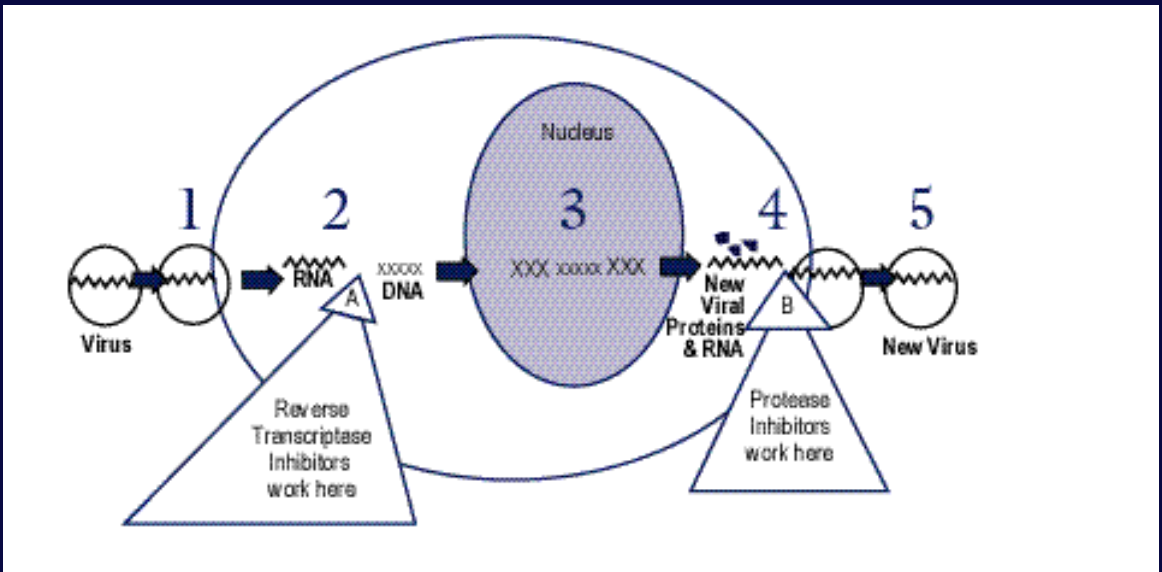
who carried virus that had become resistant to the drug. As a result of these NIAID-supported studies, combination therapy emerged as the preferred treatment modality for HIV infection.

A New Class of Anti-HIV Drugs

Meanwhile, basic research supported by NIAID and others was providing information about additional mechanisms of HIV replication that offered new targets for anti-HIV drugs. For example, Institute-supported basic research was pivotal to discovering and defining the importance of the HIV protease enzyme, which is used by the virus to produce infectious HIV particles. Other Institute-supported scientists helped determine the precise three-dimensional structure of HIV protease, a crucial step in designing drugs that block the action of the enzyme. NIAID also supported researchers who helped drug-screening efforts by developing simple, rapid tests to measure the inhibition of protease activity. Many of these basic research advances were made by investigators of NIAID's National Cooperative Drug Discovery Groups for Treatment of HIV program, which encourages collaboration among scientists from academia, industry, and government.

These accomplishments set the stage for the Institute's successful collaboration with the pharmaceutical industry in developing the new class of anti-HIV drugs known as protease inhibitors. Building on these findings, NIAID actively promoted the protease enzyme as a potential target for drug development and supported pharmaceutical companies' initial drug discovery efforts throughout the late 1980s and early 1990s. The Institute worked closely with several industrial partners as they designed, produced, and clinically tested protease inhibitors. This collaboration helped speed

Anti-HIV Drugs



The diagram above shows (1) the virus entering the cell, (2-3) conversion of viral RNA to DNA using the enzyme reverse transcriptase and incorporation of the viral genome into the DNA of the host cell, (4) viral proteins cleaved by protease for assembly of new viral particles, (5) new virus particles budding from the surface of the host cell. It also shows the steps in the viral life cycle that are interrupted by (A) reverse transcriptase inhibitors and (B) protease inhibitors.

product development. The first licensed protease inhibitor went to market in December 1995. Additional protease inhibitors were approved in 1996 and 1997.

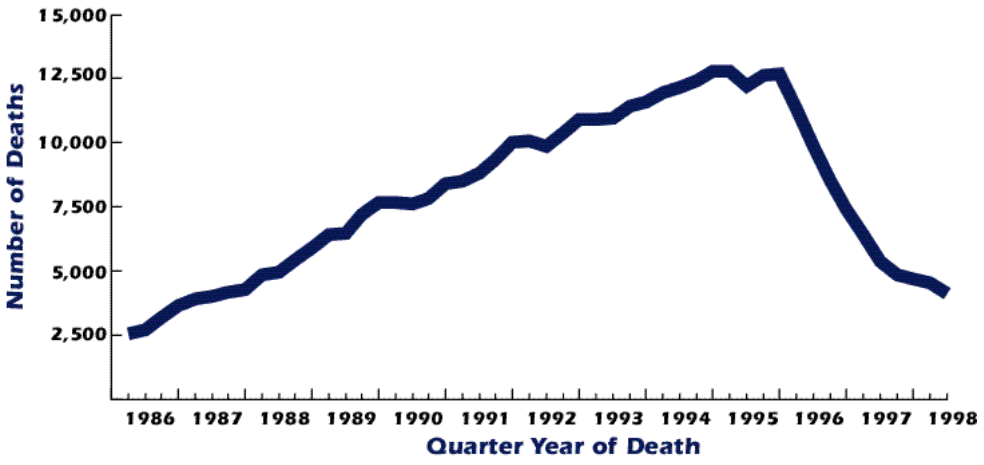
Potent Combination Therapies

Because two-drug combination therapy was proven more effective than monotherapy, the next logical step was to test three-drug combinations that included the new protease inhibitors. Since 1996, several NIAID-supported research groups and collaborating pharmaceutical companies reported that triple-drug combinations with a protease inhibitor reduced the levels of HIV circulating in the blood so dramatically that the virus often was undetectable with standard tests. In papers published in September 1997, investigators supported by the Institute conclusively demonstrated that triple-drug combinations with a protease inhibitor and two other anti-HIV drugs were more effective than one- or two-drug regimens for long-term suppression of HIV.

New Avenues for Therapies

The success in many patients of the new combination therapies, when used according to Federal guidelines, has been encouraging, at least in the short term. These heartening results, however, are not the end of the story. HIV's ability to mutate and become resistant to currently available drugs is a persistent threat, and many patients do not benefit from or cannot tolerate complex combination regimens. NIAID is supporting research to develop more potent therapies that have fewer toxic effects and are easier to administer. Also crucial are less expensive treatments for the more than 30 million persons worldwide who are infected with HIV.

AIDS Deaths in the United States From January 1986 to June 1998



Estimates Adjusted for Reporting Delays
Data Reported to CDC through December 31, 1998

The increased use of potent combinations of anti-HIV drugs has led to a significant decline in AIDS deaths in the United States in the past 2 years.

Spinoffs From NIAID Research on HIV/AIDS

NIAID basic and clinical research on HIV/AIDS has contributed to "spinoff" advances in other areas of research. Information about viruses, infectious microbes, and the immune system gleaned from HIV/AIDS research is providing insights on new ways to fight other diseases.

- Methods used to design drugs that target different phases of the HIV life cycle are being applied to the development of drugs to treat other viral diseases such as hepatitis C, influenza, and cytomegalovirus (CMV) infections.

- The successful strategy of using combination drug regimens to fight HIV is being applied to other viral diseases such as hepatitis B and C.

- The anti-HIV drug lamivudine was recently licensed in the United States for treatment of chronic hepatitis B. The drug has been approved for this purpose in several other countries, including China.

- Research to develop treatments for opportunistic infections in HIV-infected persons has produced new treatments to prevent and control diseases such as CMV retinitis, *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, cryptococcal meningitis, and herpes simplex. Many of these therapies are now used by individuals with immune systems weakened by treatments for cancer or transplants.

- Findings from a collaborative study about the effectiveness of a short-course TB prevention regimen offer hope for reducing the risk for TB in persons infected with HIV. The short-course regimen has the potential for reducing the cost of TB prevention programs, improving compliance with the prophylactic regimen, and possibly treating latent TB infection in HIV-negative individuals.

- An African study testing antibacterial washes as a means of preventing HIV transmission from mother to infant yielded unexpected results. The inexpensive antiseptic, which was applied to the mother's birth canal during labor and to the newborn immediately after birth, generally did not reduce HIV transmission. However, the washes did reduce the number of deaths related to infections as well as the rate of infections in both mothers and newborns.

- Sensitive and rapid techniques developed or refined for the diagnosis and monitoring of HIV infection are now being used for other diseases such as hepatitis, TB, Lyme disease, herpes simplex, and encephalitis.

- Retroviral vectors derived from HIV/AIDS research are being adapted for use in gene transfer therapy for cancer patients. Scientists also are investigating gene-based therapies to help patients with hepatitis and chronic granulomatous disease.

These concerns underscore the need for NIAID's continued effort to find new therapies for HIV infection. Basic researchers at NIAID laboratories have helped explain why HIV can rebound in patients who discontinue combination therapy, and they are working to develop new ways to attack pools of latently infected cells that serve as hiding places for HIV. NIAID scientists also have opened new avenues for therapies with the discovery of coreceptors for HIV's entry into immune cells. (See the story of discovery on page 19.)

Since 1993, NIAID's Strategic Program for Innovative Research on AIDS Treatment (SPIRAT) has supported basic and clinical research on novel approaches to treatment. Scientists supported by SPIRAT and other NIAID research programs are contributing to the discovery and development of the next generation of anti-HIV treatments. Such strategies may include therapies that combat drug resistance by targeting a broader range of mechanisms in the HIV replication cycle, treatments designed to rebuild the damaged immune system of infected individuals, and gene therapy to protect cells from HIV infection or interfere with HIV function in already infected cells. NIAID also plays a central role in international efforts to develop an HIV vaccine. As the story of the AIDS epidemic continues to unfold, NIAID research will continue to provide the foundation for new breakthroughs in improving the quality and duration of life for people infected with HIV.

Chemokines and HIV Coreceptors: Opening Doors to New Anti-HIV Strategies

NIAID's sustained commitment to basic research continues to yield breakthroughs that, although still in their early stages, are likely to culminate in significant medical benefits. The story of chemokines and HIV coreceptors is an example of how years of basic research in seemingly different fields can rapidly and unexpectedly converge to produce insights with profound implications for future research and treatment. By uncovering the role that chemokines and their receptors play in HIV infection, investigators at NIAID have greatly advanced our understanding of how the virus enters immune cells. Continued work in this area has the potential for uncovering new strategies for preventing and treating HIV infection.

Since the discovery of HIV in 1983, scientists have been looking for the answers to two critical, but apparently unconnected, questions about the virus. The first question focused on finding substances produced by the immune system that could suppress HIV replication. The second question involved the identification of additional receptors or other mechanisms that play a part in HIV entry into immune cells.

The Search for HIV Suppressor Factors

One step toward answering the first question was taken in 1986, when NIAID-supported basic researchers found that immune cells called cytotoxic T lymphocytes (CTLs) secrete substances capable of suppressing HIV replication in cells grown in the laboratory. The same researchers supported this discovery with the finding that persons with HIV infection who did not develop symptoms of the disease for long periods of time had relatively high levels of CTLs in their blood. However, 10 years passed before the specific molecules or factors responsible for this suppression were identified.

In 1987, scientists studying basic immunology discovered the first of a family of molecules, collectively named chemokines, that play a role in activating the immune system's response to infection. These signaling molecules attach themselves to specific binding sites (receptors) on immune cells, trigger the cells to respond to infection, and call more immune cells to infected areas to fight invading microbes.

It was not until December 1995, however, that the connection between chemokines and HIV infection became clear. Researchers at NIH's National Cancer Institute (NCI) discovered that CTLs secrete certain chemokines that can suppress HIV activity. Three specific chemokines—RANTES, MIP1-alpha, and MIP1-beta—were found to work together to block HIV replication. Scientists at NIAID determined that other substances, or suppressive factors, secreted by CTLs also must be involved in HIV suppression. Since this discovery, researchers have found additional chemokines that suppress HIV replication and continue to work on identifying still other suppressive factors.

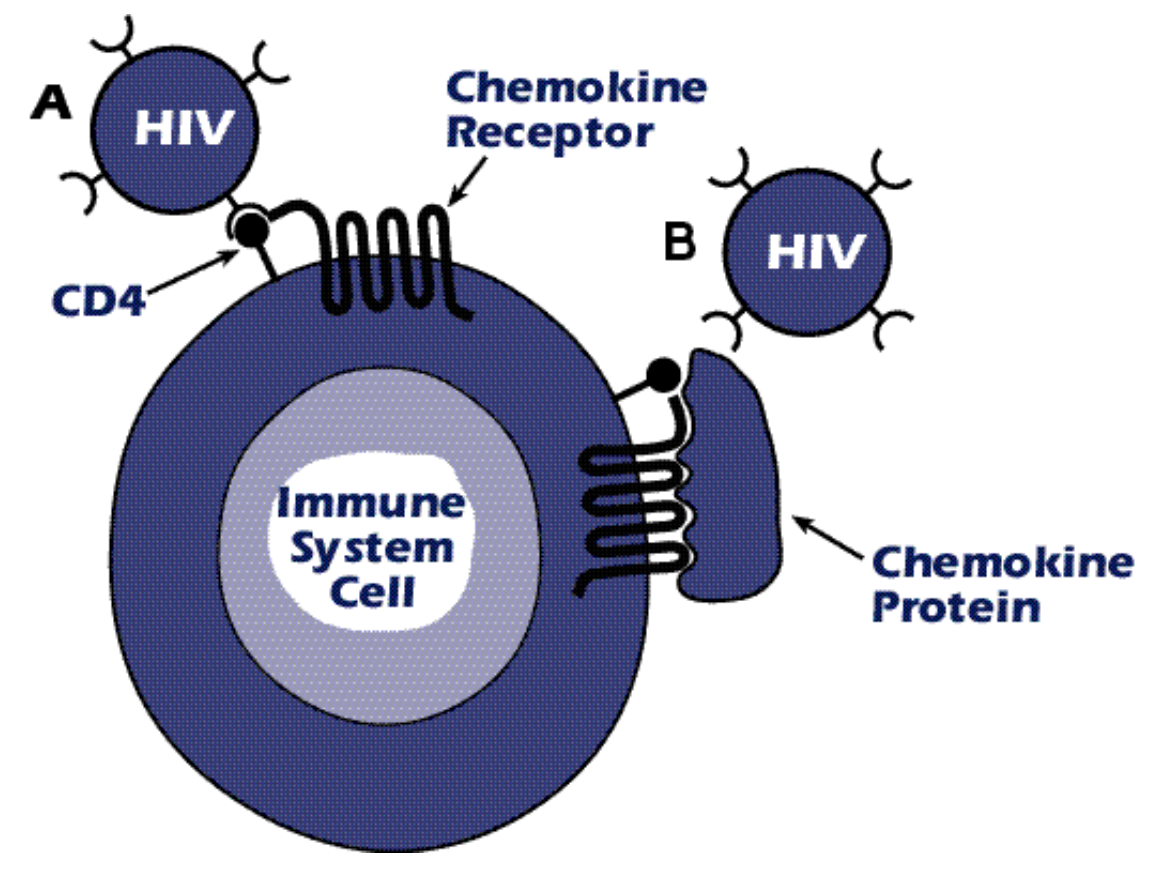
The Search for HIV Coreceptors

As scientists continued their endeavors to better understand the role of CTLs in HIV suppression, other investigators were following a very different path of inquiry. For more than a decade, AIDS researchers had known that a specific molecule, or receptor, on the surface of immune cells allowed HIV to enter cells. Studies in animals, however, indicated that this molecule, called CD4, alone was not sufficient—some other molecule or molecules were involved in HIV infection of immune cells.

In 1994, researchers at NIAID developed an innovative test for studying HIV fusion with immune cells. Information obtained from this test led to the discovery in April 1996 of a second receptor needed for the entry of HIV into cells. Researchers named the newly identified receptor "fusin" (CXCR4) because it enables certain strains of HIV to fuse with and enter immune cells called T cells. An analysis of the structure of fusin revealed that it was a receptor for chemokines, the family of signaling molecules that includes beta-chemokines, which the previous December were shown to suppress HIV activity.

Just 1 month after the discovery of fusin, researchers from two collaborating NIAID laboratories found a second chemokine receptor, called CCR5, that was necessary for the entry of HIV into immune cells called macrophages. This receptor was already known to be the binding site for the chemokines recently found to play a pivotal role in suppressing HIV infection. The new findings suggest that the three chemokines suppress HIV replication by binding to the same receptors needed by certain strains of HIV to enter immune cells.

Chemokine Blockade of Coreceptors for HIV



To enter a cell, HIV must attach to a CD4 molecule and a chemokine receptor on the surface of the cell as depicted at A. When the chemokine receptor is occupied or defective, HIV cannot attach to the cell because the second interaction is physically blocked as depicted at B.

Insights on Resistance to HIV Infection

The discovery of these and other HIV coreceptors by NIAID researchers gave investigators new information that would allow them to tackle another longstanding question about HIV. Scientists have questioned for years why some individuals do not become infected with HIV despite repeated exposure to the virus. NIAID-supported researchers were spurred by the coreceptor breakthroughs to analyze blood samples from persons at high risk of contracting HIV, probing specifically for molecular differences between those who were infected and those who had been repeatedly exposed but somehow remained uninfected. These investigators quickly discovered that seemingly resistant individuals received two mutated copies (one from each parent) of the gene for CCR5, resulting in the lack of a functional CCR5 binding site on their immune cells. Without this coreceptor, HIV could not enter their cells. Researchers also found that HIV-infected individuals who had received a copy of the defective CCR5 gene from only one parent progressed more slowly to AIDS than those who had two normal copies of the gene. Because these mutations do not account for all cases of resistance to HIV infection, scientists are looking for other possible factors, including genetic defects involving other coreceptors.

Future Anti-HIV Strategies

Scientists already are exploring innovative treatment and vaccine strategies based on the leads provided by NIAID researchers. For example, it might be possible to treat HIV infection by developing drugs that block the coreceptors needed for HIV entry. Vaccines that trigger the activity of immune cells that inhibit the binding of HIV to coreceptors may be able to prevent infection. Although still in its early stages, the development of therapies and vaccines based on chemokine receptors promises to strengthen a growing arsenal of weapons for use in fighting HIV.

Immune Tolerance: Improving Transplantation Success

In the past decade, discoveries made by NIAID-supported scientists about the mechanisms that activate and regulate the immune response have yielded a new approach to preventing transplant rejection. Rather than suppressing the entire immune system, this new approach uses a targeted strategy designed to induce tolerance (the lack of an immune response) by turning off the specific immune cells that attack the transplant. Although more research is needed to develop therapies, NIAID-supported research on immune tolerance is contributing to the eventual development of ways to improve transplant success and of new treatments for a wide range of immunologic disorders.

Each year more than 19,000 transplants are performed in the United States. An additional 56,000 critically ill people in this country are waiting to receive an organ transplant that could forestall further disability or death from conditions such as heart disease, kidney failure, liver disease, and diabetes. Although advances derived from transplantation research have improved rates of transplant success and patient survival, problems such as complications from immunosuppressive therapy remain to be solved.

Transplant Rejection and Early Prevention Strategies

Since the first successful organ transplant was performed in the United States in 1954, one of the most serious problems facing transplant patients has been the possibility that their own bodies will try to reject or destroy the transplant. Rejection is part of the body's natural reaction to foreign invaders. A person's cells are tagged with surface molecules called major histocompatibility antigens (MHA). Much like fingerprints, MHAs are unique to an individual. Thus, when a person receives a transplant, his or her immune system identifies the foreign tags (MHAs) on the transplant and proceeds to rid the body of, or reject, the transplant. To reduce the risk of rejection, physicians try to find donors whose MHAs are as genetically close to those of the recipient as possible. Nevertheless, most transplants, with the exception of those donated by identical twins, are recognized by the patient's immune system as foreign. Rejected transplants need to be surgically removed, and if the transplant is a life-sustaining organ such as a lung, liver, or heart, a patient may die before a replacement organ is found.

In the past few decades, transplantation research has focused on identifying and understanding the mechanisms of transplant rejection so that it can be prevented and survival can be prolonged. Among the most important advances has been the development of drugs that help prevent transplant rejection by suppressing the patient's immune system. NIAID-supported research led to the discovery and licensing in 1983 of cyclosporine, the first immunosuppressive drug for transplant patients. Cyclosporine and other immunosuppressive drugs have greatly increased the short-term success rate, particularly of kidney and other solid organ transplants. Unfortunately, these drugs are highly toxic and require adherence to a lifelong regimen that suppresses the entire immune system, thereby increasing the susceptibility of patients for developing infections, cancer, and other complications. Moreover, immunosuppressive drugs have not had a significant effect on increasing long-term transplant survival. More than half of transplanted kidneys, the organ most often transplanted, are rejected

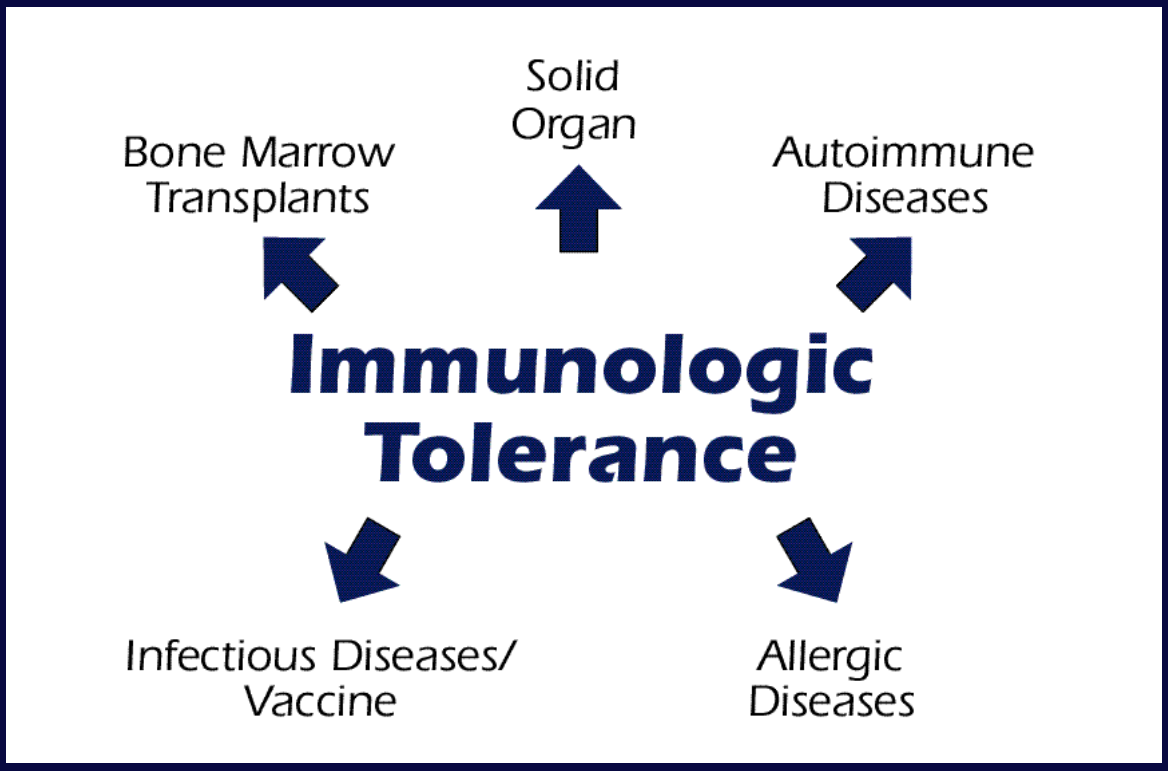
within 10 years, and the patient must receive another kidney transplant or start dialysis treatments, which are uncomfortable, expensive, and time-consuming.

New Approaches to Preventing Rejection

NIAID-supported basic researchers have made major contributions to advances in understanding and preventing transplant rejection. One new approach to promoting long-term survival is selectively blocking the immune response that leads to rejection of transplanted organs, tissue, or cells. Scientists recently discovered that, in addition to the MHAs, other molecules, called costimulatory molecules, are involved in immune tolerance. Using knowledge gained through a series of basic discoveries involving these costimulatory molecules, scientists are working to develop strategies to induce tolerance to transplanted organs and tissues.

In 1991, NIAID-supported basic researchers identified a molecule (called CD28) on the surface of certain immune system cells that was involved in the immune response to transplanted tissues or organs. During the following 4 years, scientists demonstrated that blocking

Immunologic Tolerance



Advances in tolerance induction will provide valuable new therapeutic strategies in transplantation and in treating a wide range of immune-mediated disorders.

the activity of CD28 inhibited immune system responses crucial to transplant rejection. In 1994, researchers identified CD40 as another cell surface molecule involved in the immune system response to transplants. A strategy emerged for inducing transplant tolerance by blocking the signals that these "costimulatory" molecules deliver to initiate an attack on a foreign tissue or organ.

Building on the discovery of these and other costimulatory molecules, NIAID-supported scientists developed animal models to determine whether blocking the activation of CD28 and CD40 signals can prevent transplant rejection *in vivo* (in the living body of an animal). In 1996, researchers sponsored by NIAID succeeded in prolonging the survival of skin and heart transplants in mice using this strategy, without the need for standard continuous therapy that globally suppresses the immune system. The following year, investigators at the Department of Defense used the same approach to achieving tolerance to kidney transplants in monkeys, a model that closely resembles human transplantation. While this approach to controlling the immune system prevents rejection, it leaves intact the ability to fight infections and is much less toxic than conventional immunosuppressive therapy. Blocking immune cell signals has the potential for addressing other problems faced by transplant patients. For example, in 1998, NIAID-supported scientists found that a costimulation blockade prevented graft-versus-host disease (GVHD) in patients who received bone-marrow transplants. GVHD occurs when transplanted immune cells attack the healthy cells of the recipient, causing life-threatening illness.

Future Challenges and Opportunities

NIAID is supporting studies of other strategies for inducing immune tolerance. These innovative approaches include manipulating immune system messenger molecules called cytokines and triggering the suicide of the specific immune cells that normally would attack the transplant. Additional research is needed to determine how long transplant survival can be extended by using these strategies. The next challenge is to translate the information on immune tolerance obtained from experimental models into the development of safe and effective therapies for humans. Promising results in animal models and early human studies suggest that therapies involving tolerance induction have the potential to prevent transplant rejection without the use of immunosuppressive drugs. The ability to induce immune tolerance also holds promise for treating immunologic disorders, including autoimmune diseases, which result when immune tolerance of the body's own cells fails. For example, multiple sclerosis is an autoimmune disease that results when the immune system attacks nerve cells. Therapies that could restore immune tolerance to self tissue would be valuable tools in treating this debilitating disease and other autoimmune diseases.

NIAID has developed a comprehensive plan to capitalize on the opportunities presented by research in immune tolerance. Collaborative and coordinated research efforts will involve basic scientists, clinical researchers, other NIH Institutes, and the pharmaceutical and biotechnology industries. The goal of this plan is to enhance knowledge about immune tolerance and to speed the translation of basic research discoveries into clinical approaches to treating and preventing immunologic diseases. This effort has led to the first human trial, cosponsored by NIAID and Biogen, to test immune tolerance strategies in people receiving kidney transplants.

Selected NIAID Research Priorities

NIAID basic research efforts have provided the foundation for medical discoveries that have saved the lives of millions. When determining its research priorities, NIAID considers many factors such as the impact of diseases on the public health, developments in technology that could be used to develop new prevention techniques or treatments, and the research opportunities in a particular field. In some cases, for example research related to bioterrorism defense, NIAID has increased its research efforts in response to a national need identified by the President and the Congress. This section briefly describes some selected priority areas of NIAID research (in addition to those noted in the context of the stories of discovery).

Global Health. NIAID-supported researchers are actively working on unlocking the secrets of diseases such as HIV infection, malaria, TB, and diarrheal diseases, which occur all over the world. The NIAID research program is based on the view that the United States is a part of a global community where millions of people cross international borders every day. Given that travel from as far away as Australia takes less than a day, a new infectious agent could easily spread in mere hours from one continent to another. NIAID is committed to basic and clinical research to lower the opportunities for disease transmission and to increase the capacity to diagnose and treat infectious diseases.

Emerging and Reemerging Diseases. More than 30 new diseases have appeared in the last 20 years, including HIV/AIDS, Lyme disease, H5N1 avian influenza, hepatitis C, and infections caused by the Hantavirus, Ebola virus, and *Cryptosporidium*. Several diseases previously thought to have been conquered, such as TB and malaria, have reemerged and are becoming more difficult to control. NIAID's International Centers for Tropical Disease Research network is contributing to the scientific infrastructure needed to respond rapidly to new and reemerging diseases as they are detected around the globe. NIAID, other NIH Institutes, and agencies such as the CDC focus on the threat of new and reemerging diseases by tracking disease outbreaks, providing diagnostic and laboratory tools, and performing the basic research to facilitate the development of effective vaccines and treatments.

Drug Resistance. Many serious infections are becoming resistant to standard drug treatments. For example, drug-resistant TB and malaria are major killers worldwide. NIAID scientists are developing new and improving current treatments to counter drug-resistant strains of *Salmonella typhimurium, Staphylococcus aureus, Mycobacterium tuberculosis, Campylobacter jejuni,* and *Plasmodium falciparum,* the microbe that causes malaria, as well as many other infectious microbes. Basic researchers are studying the causes of drug resistance, how it can be prevented, and what can be done to counteract it.

Hepatitis C Virus (HCV). Each year, an estimated 10,000 Americans die from HCV, a leading cause of chronic liver disease and cirrhosis. About 4 million people are chronically infected in the United States alone, with about 1,000 of these people requiring liver transplants each year. Basic research scientists are making progress in deciphering the structure and genetic makeup of HCV and in understanding how the virus works, how it is transmitted, and how the human body responds to the infection

over many decades. In 1997, researchers discovered that the drug interferon alpha may effectively treat HCV infection in some patients. NIAID is exploring collaborative clinical trials on HCV through the Collaborative Antiviral Study Group.

Vaccine Development. NIAID researchers are working on developing dozens of new vaccines. Vaccines against HIV/AIDS, malaria, herpes simplex, *E. coli*, CMV, dengue fever, HCV, hepatitis E virus, TB, cholera, leishmaniasis, and human papillomavirus are in various stages of development, ranging from the first basic research steps to the final testing phases. Because malaria and TB affect millions of people throughout the world, NIAID developed the Malaria Vaccine Research Plan and the TB Vaccine Blueprint to facilitate development of these critically needed vaccines. Clinical researchers use basic research findings to develop safer and more effective vaccines, such as the acellular vaccines recently developed for pertussis. With its partners in industry and academia, NIAID is exploring new vaccination delivery technologies, such as edible vaccines and a vaccine delivered through a nasal spray.

NIAID-supported scientists recently found that an edible vaccine delivered in potatoes to people elicited an immune response against *E. coli*. In an NIAID-supported study, a nasal spray influenza vaccine administered to children provided greater than 90 percent protection

Nasal Spray Vaccine

A new influenza vaccine sprayed as a fine mist into children's noses is highly effective at preventing both the flu and flu-related ear infections. The new vaccine called FluMist™ is being developed for both children and adults under a cooperative research and development agreement between the biopharmaceutical company Aviron and NIAID. Aviron anticipates submitting an application for licensure of FluMist™ to the Food and Drug Administration later this year.

Credit: Aviron

against influenza. Unexpectedly, this vaccine also protects against ear infections that result from influenza.

Autoimmune Diseases. Autoimmune diseases, including rheumatoid arthritis, type-I diabetes, and multiple sclerosis, afflict an estimated 5 percent of the U.S. population. The human and financial burden of these diseases is immense. Autoimmune diseases occur when the immune system mistakenly attacks the body's own tissues and organs. Years of basic research on the immune system recently culminated in a new strategy that shows promise for the induction of tolerance in autoimmune diseases (see Tolerance story). To accelerate the development of this and other new therapies and to enhance our understanding of autoimmune diseases, NIAID and other NIH Institutes have galvanized efforts to address a broad spectrum of research questions including the roles of environmental, infectious, and genetic factors in autoimmune diseases, as well as innovative therapies such as islet cell transplantation for type-I diabetes.

Research Related to Bioterrorism Defense. NIAID's mission and expertise in infectious diseases ideally position it to help prepare the Nation against potential bioterrorist attacks. NIAID historically has conducted research on several infectious agents that have been identified as potential agents for use in bioterrorist attacks. In addition, NIAID conducts and supports research on the development of therapeutics and vaccines for pre- and post-exposure prophylaxis and treatment for a wide variety of infectious agents, including several of those identified as potential biological weapons. As part of the President's new initiatives related to bioterrorism preparedness, the Institute has expanded basic research on several infectious pathogens that might be used in bioterrorism attacks. Further, in coordination with other Federal agencies, the Institute recently established a research agenda for the rapid development of diagnostic tools, treatments, and vaccines for diseases that may be caused by biological weapons.

Food Safety and Water Contaminants. Public concerns about the safety of food and drinking water in the United States are increasing as a result of recent disease outbreaks. Approximately 80 million cases of illness resulting from food or water contaminated with culprits such as *E. coli*, *Campylobacter, Salmonella,* hepatitis A, and other microbes occur in the United States each year. To improve the safety of our food and water, NIAID basic researchers study the biology and genetics of more than 50 types of water or food-borne organisms, and the results are used to develop new prevention and treatment strategies. For example, NIAID scientists were instrumental in the development of a vaccine to prevent hepatitis A.

The Role of Infectious Diseases in Chronic Conditions. Basic research has discovered that some microorganisms may play a major role in certain chronic diseases. For example, the bacterium *Helicobacter pylori* causes ulcers and may contribute to stomach cancer. Both hepatitis B and hepatitis C can lead to chronic liver disease and liver cancer, and the human papillomavirus is responsible for most cases of cervical cancer. Rheumatoid arthritis has been linked to infections of *E. coli, Shigella flexneri,* and other bacteria. Other infectious agents have been linked to athlerosclerosis and Crohn's disease, and Guillain Barré syndrome has been associated with prior diarrheal disease caused by *Campylobacter jejuni*. As basic research reveals more links between infectious agents and chronic illnesses, NIAID will be at the forefront of developing new methods of treatment and prevention.

Asthma and Allergic Diseases. Allergic diseases are among the major causes of illness and disability in the United States, affecting as many as 40 to 50 million Americans and resulting in high medical costs and absenteeism from work and school. Like autoimmune diseases, allergies are caused by immune system malfunctions. NIAID conducts and supports research to improve methods for diagnosing, treating,

and preventing allergies and asthma and to better understand the causes and mechanisms of allergic reactions. This research includes basic studies on the immune system and studies to identify genes that make people susceptible to asthma and allergies. Many of these studies are conducted at the 12 Asthma, Allergic, and Immunologic Diseases Cooperative Research Centers throughout the country. Also, because asthma disproportionately affects socioeconomically disadvantaged people, particularly children, NIAID and the National Institute of Environmental Health Sciences support the National Cooperative Inner-City Asthma Study. This ongoing study is evaluating an asthma intervention program that emphasizes physician education and cost-effective measures for improving the indoor environment to reduce asthma severity among inner-city children.

New Technologies. NIAID and the National Aeronautics and Space Administration (NASA) are collaborating to test the public health utility of two new breakthrough technologies: satellite-based remote sensing technology and geographic information systems. By comparing geographic and weather information collected by a satellite with data collected on the ground using the geographic information systems computer program, scientists may be able to predict outbreaks of infectious diseases. This technique was used to predict outbreaks of Lyme disease by pinpointing geographic areas where conditions were conducive to tick breeding. Another new technology, aerial multispectral videography, uses airplane-mounted cameras to measure electromagnetic radiation reflected from objects in the environment. For example, aerial multispectral videography identified illegal tire dumps, which are breeding grounds for disease-carrying mosquitoes. NIAID is developing programs to inform researchers and public health officials about these and other new technologies and their potential uses.

Genome Sequencing. Advances in *recombinant DNA technology* have led to the development of automated techniques to rapidly sequence the genetic makeup of infectious microbes. NIAID researchers and other scientists use this knowledge to identify targets for new drugs or vaccines, to understand the molecular basis of drug resistance, and to improve diagnostic tests. Recently, NIAID-supported researchers sequenced two important microbes: *Chlamydia trachomatis*, a virulent sexually transmitted organism that causes infertility and blindness, and *Treponema pallidum,* the cause of syphilis. In addition, one chromosome of the malaria parasite, *Plasmodium falciparum,* was sequenced with NIAID support. Altogether, the Institute sponsors the sequencing of about 20 microbes.

Conclusion

The stories of discovery in this booklet demonstrate how ongoing support for basic research can yield important medical innovations—such as protease inhibitors—and open new, promising areas of inquiry—such as tolerance induction for preventing transplant rejection and autoimmune diseases. As these stories relate, answering a few fundamental scientific questions, such as identifying some critical molecules on HIV, can trigger a cascade of discoveries that unexpectedly solve a problem that has been puzzling researchers for years. Although the ultimate payoffs of NIAID-supported basic research are the vaccines, treatments, and other public health tools that reduce the burden of infectious and immunologic diseases, equally important benefits include the formulation of new scientific questions and new directions for research that can lead to future medical breakthroughs.

As NIAID enters the 21st century, it will continue to identify and pursue research opportunities and priorities that address current and potential public health problems. Through its sustained commitment to basic research and cross-sector collaborations, NIAID will help translate scientific insights into practical applications that improve the health of Americans and people around the world.

Basic Researcher in the Laboratory